REMARKS

I. Claim Status

Claims 11-16 are pending. The Examiner has withdrawn claims 14-16 from consideration as being directed to a non-elected invention. Dec. 11, 2009, Final Office Action at 2. No claims are amended herein. Thus, no new matter has been added.

Applicants respectfully acknowledge that the Examiner has withdrawn the rejection of claims 14-16 under 35 U.S.C. § 112, ¶ 2, and § 101, and the rejection of claim 15 under 35 U.S.C. § 112, ¶ 1. Dec. 11, 2009, Final Office Action at 3-4.

II. Rejection Under 35 U.S.C. § 103(a)

The Examiner has maintained the rejection of claims 11 and 12 under 35 U.S.C. § 103(a) as unpatentable over Blaakmeer et al., "Structure-Activity Relationship of Isolated Avenanthramide Alkaloids and Synthesized Related Compounds as Oviposition Deterrents for *Piers Brassicae*," Journal of Natural Products, 57(8):1145-51 (1994) ("Blaakmeer") in view of Appeldoorn et al., "Rational Optimization of a Short Human P-selectin-binding Peptide Leads to Nanomolar Affinity Antagonists," Journal of Biological Chemistry, 278(12):10201-207 (2003) ("Appeldoorn"), and Patani et al., "Bioisosterism: A Rational Approach in Drug Design," Chem. Rev., 96:3147-76 (1996) ("Patani"), for the reasons set forth on pages 4-12 of the December 11, 2009, Final Office Action.

Applicants respectfully traverse this rejection for the reasons of record and for the following additional reasons.[1]

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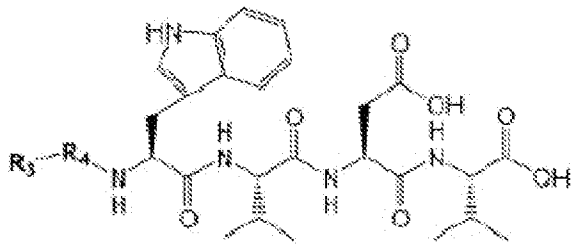
[1] In their prior response, Applicants identified the following Y' substituent in the claimed compounds

The Examiner states that it would have been obvious to modify compound 10 disclosed in Blaakmeer by replacing the two hydroxy substituents on the phenyl ring of the amine-part of the structure with hydrogens based on the teachings of Appeldoorn and Patani. Applicants respectfully disagree.

First, with respect to Appeldoorn, the Examiner states that "Appeldoorn teaches pentapeptide core motif as potent antagonists for P-selectin using two-step combinatorial chemistry approach," and "[t]hese compounds with the number of exposed hydroxyl groups on the first ring appear to be critical for its affinity, because monobenzoic acid derivatized and dihydroxybenzoic acid derivatized were much less effective than the trihydroxylated counterparts." Dec. 11, 2009, Final Office Action at 6 (citing Appeldoorn at 10205). The core compound referred to in this part of Appeldoorn has the following structure:

A



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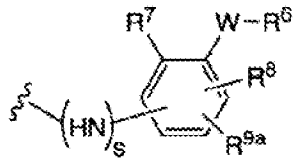
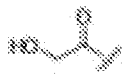
(R_3-R_4-WVDV-OH)



and mistakenly stated that "the carboxylic group (i.e., W is -$(CH_2)_v$-, v is 0, and R^6 is CO_2H), if chosen, may **not** be in the ortho-position ...." Applicants wish to clarify that the –W-R^6 group can be in any position, including the ortho-position. Applicants' remaining arguments in the prior response still support a conclusion of non-obviousness.

Appeldoorn at 10204. The monobenzoic acid-derivatized peptides of compound 14 in Figure A in Appeldoorn were substituted by the following acyl modifications:



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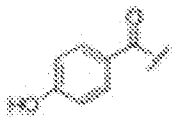

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the dihydroxybenzoic-acid derivatized peptide was substituted by the following acyl modification:

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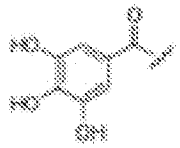
and the trihydroxylated counterpart was substituted by the following acyl modification:



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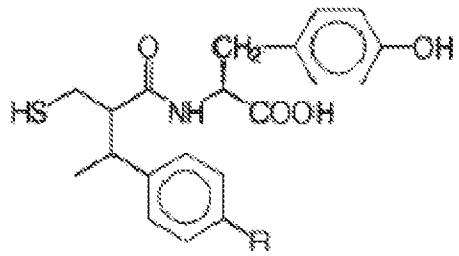
Appeldoorn at 10204-10205. As is readily apparent, the structure of the mono-, di-, and trihydroxybenzoic peptides of compound 14 in Figure A in Appeldoorn differ significantly than the structure of compound 10 in Blaakmeer. For this reason, one of skill in the art would not have looked to Appeldoorn to modify the structure of compound 10 in Blaakmeer.

Even assuming for the sake of argument that one of skill in the art would have considered Appeldoorn to modify compound 10 in Blaakmeer, which Applicants do not

concede, the skilled artisan would not have been motivated to replace the hydroxy groups of compound 10 with hydrogens, for example. Indeed, as the Examiner acknowledges, Appeldoorn states "monobenzoic acid-derivatized (acids 23 and 24) and dihydroxybenzoic acid-derivatized (acid 25) peptides were much less effective than the trihydroxylated counterparts (1) (Fig. 4*D*)." Appeldoorn at 10205 (emphasis added). Thus, Appeldoorn teaches one of skill in the art away from modifying compound 10 of Blaakmeer in the way that the Examiner suggests, and, rather, would have taught the skilled artisan to maintain the two hydroxy groups on compound 10 or even add a third hydroxy group. M.P.E.P. § 2141.02(VI) ("A prior art reference must be considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention.") (citation omitted).

Second, with respect to Patani, the Examiner states that it would have been obvious to use combinatorial chemistry to modify compound 10 of Blaakmeer since "Patani suggests monovalent substitution by hydroxyl group in place of hydrogen." Dec. 11, 2009, Final Office Action at 7 (citing Patani at 3152, Table 9). Applicants agree that Patani states, "Monovalent substitution by fluorine, hydroxyl, and amino in place of hydrogen has recently been used in the design of these metallopeptidase inhibitors (Figure 11, Table 9)." Patani at 3152. The compound disclosed in Figure 11, Table 9 has the following structure:



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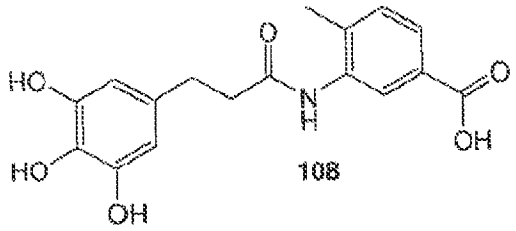
Again, compound 17 of Patani is significantly different structurally then both compound 10 of Blaakmeer and compound 14 of Appeldoorn. For this reason, one of skill in the art would not have looked to Patani to modify the structure of compound 14 of Appeldoorn, much less compound 10 in Blaakmeer.

Moreover, as the Examiner acknowledges, Patani suggests replacing hydrogen in compound 17 with fluorine, hydroxyl, and amino. Thus, even assuming for the sake of argument that one of skill in the art would have considered modifying compound 10 of Blaakmeer based on the teachings of Patani, which Applicants do not concede, the skilled artisan would not have been motivated to make the opposite modification – replacing the hydroxyl groups on compound 10 of Blaakmeer with hydrogens. Even if one of skill in the art would have considered reversing the modification taught by Patani – replacing a hydroxyl group with hydrogen – Appeldoorn, for the reasons discussed above, teaches away from making such a modification.

Accordingly, because both Appeldoorn and Patani, individually and in combination, teach away from modifying compound 10 of Blaakmeer in a manner that results in the claimed compounds, Applicants respectfully submit that the rejection is in error and should be withdrawn.

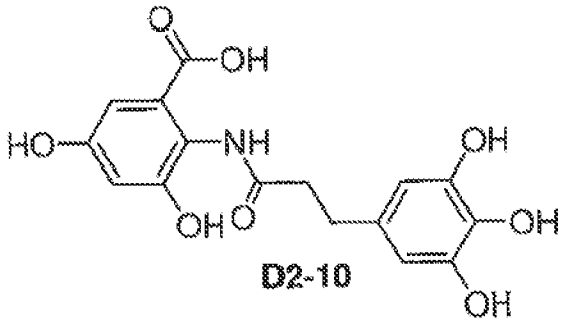
While unnecessary, to further demonstrate the non-obviousness of the claimed invention, Applicants have compared the *in-vitro* activity of a compound falling within the scope of the claims with compound 10 of Blaakmeer, which the Examiner relies upon for the obviousness rejection. Even if, as the Examiner suggests, one skilled in the art would have been motivated by Appeldoorn and Patani to modify compound 10 disclosed in Blaakmeer by replacing the two hydroxy substituents on the phenyl ring of the amine-part of the structure with hydrogens, which Applicants do not concede, the claimed invention would not have been obvious in view of these references. Indeed, nothing suggests, nor would one skilled in the art have reasonably expected, that the claimed compounds, which differ structurally from compound 10 of Blaakmeer, would possess superior *in-vitro* activity to inhibit the binding of P-, L-, and E-selectin than compound 10 of Blaakmeer, as illustrated by the attached Declaration under 37 C.F.R. § 1.132 of Remo KRANICH ("Declaration").

As described in the Declaration, the following compound corresponding to Example 108 of the present application and falling under the claims was prepared:



108

See Declaration at 2-3. The following compound D2-10, corresponding to compound 10 of Blaakmeer, was prepared as well:



D2-10

See Declaration at 3-5.[2] As can be seen, the D2-10 compound differs from the claimed compounds, including Example 108, in that it contains two hydroxy groups as substituents on the phenyl ring of the amine-part of the structure. In contrast, the claimed compounds, including Example 108, do not contain any hydroxy substituents on the phenyl ring of the amine-part of the structure. Contrary to the conclusion set forth in the rejection, it would not have been obvious to replace the two hydroxy groups of D2-10 with one of the recited substituents in the claimed invention, including replacing the two hydroxy groups with a hydrogen and methyl group as is present on Example 108.

To demonstrate that such a modification would not have been obvious, Applicants compared the compound of Example 108 with the D2-10 compound for their *in-vitro* ability to inhibit the binding of P-, L-, and E-selectin chimeric molecules to sLe^x and tyrosine-sulphate residues linked to a polymeric matrix as a PSGL-1 substitute. *See* Declaration at 5-6. As Table 1 of the Declaration indicates, the compound of Example 108 shows 20x greater ability at inhibiting all three selectins (P-, L-, and E-) than the D2-10 compound. *See* Declaration at 6 and Table 1.

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[2] Applicants note that the Office Action appears to mistakenly state that R_4 in compound 10 of Blaakmeer is CH_2=CH_2, where, in fact, R_4 is CH_2—CH_2. *See* Dec. 11, 2009, Final Office Action at 11.

The Declaration, therefore, demonstrates unexpected results for the claimed compounds. These results show that compounds according to the present claims possess greater activity in inhibiting all three selectins (P-, L-, and E-) than compounds falling outside the scope of the claims, including the D2-10 compound, i.e., the compound 10 of Blaakmeer. At the time of the invention, it would have been unexpected that compounds having the claimed structure, including the specific substituents recited for the phenyl ring of the amine-part of the structure, would significantly improve the inhibiting activity of all three selectins (P-, L-, or E-) compared with compounds that differ structurally in the substituents on the phenyl ring of the amine-part of the structure, such as the two hydroxy groups in the D2-10 compound.

Accordingly, Applicants respectfully submit that the Examiner has not established a *prima facie* case of obviousness, and the rejection should be withdrawn.

Conclusion

In view of the foregoing remarks, Applicants respectfully request reconsideration of this application and the timely allowance of the pending claims.

If the Examiner believes a telephone conference could be useful in resolving any outstanding issues, the Examiner is respectfully invited to contact Applicants' undersigned counsel at (703) 776-9703.

Respectfully submitted,

J.A. LINDEMAN & CO. PLLC

Date: May 10, 2010

By: /Aaron M. Raphael, Reg. No. 47,885/
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ATTACHMENT: Declaration of Remo KRANICH under 37 C.F.R. § 1.132